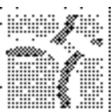


Upcoming NCIC-CTG led Breast Cancer Studies with Pharmacogenetic Studies

- MA.31 A randomized, open-label, Phase III study of Taxane-based chemotherapy with lapatinib or trastuzumab as first-line therapy for patients with HER2/ner positive metastatic breast cancer (K. Gelmon/GSK)
- MA.30* A Phase III, randomized controlled trial of anastrozole compared to anastrozole + fulvestrant as adjuvant endocrine therapy for postmenopausal women with ER/PR+ breast cancer (K. Pritchard/AZ)

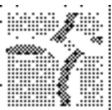
* On hold, pending data from closed European trial



MA.31 Schema

ELIGIBILITY CRITERIA

- **Her2/neu + metastatic breast cancer**
- **No Prior chemo or anti-Her2/neu for metastatic treatment**



MA.31 Schema

← Weeks 1-24 →

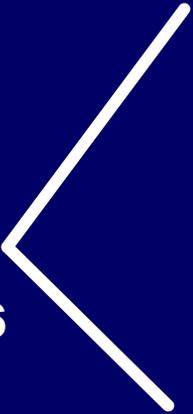
Lapatinib 1250 daily

+

Paclitaxel 80 D1,8,15 q28d

OR Docetaxel 75 q21d

Her2/
neu+
N=536



MA.31 Schema



Lapatinib 1250 daily

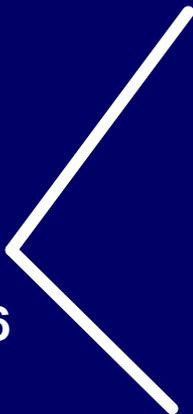
+

Paclitaxel 80 D1,8,15 q28d

OR Docetaxel 75 q21d

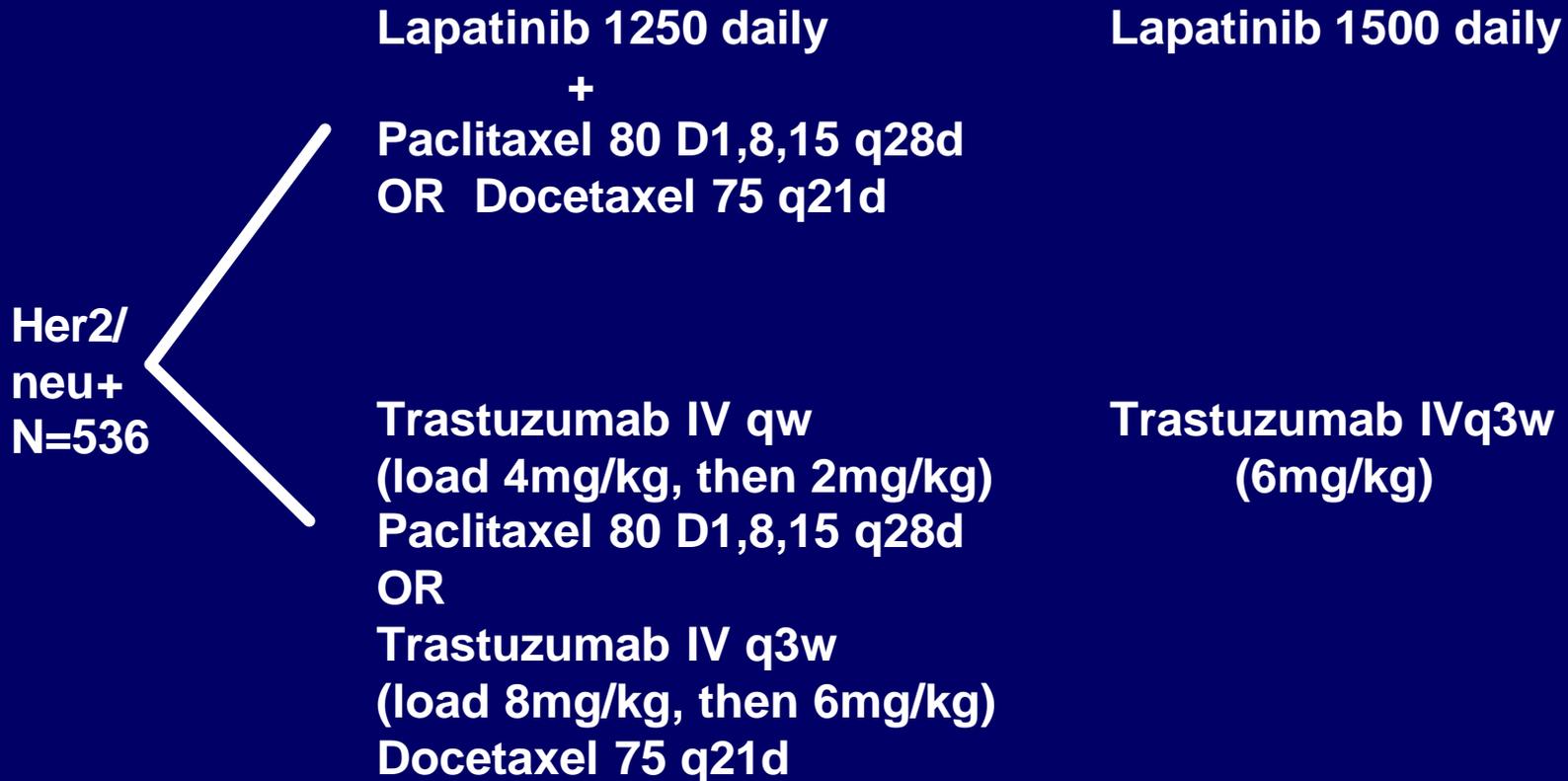
Lapatinib 1500 daily

Her2/
neu+
N=536



MA.31 Schema

← Weeks 1-24 → ← Maintenance →



MA.31 Schema

← Weeks 1-24 → ← Maintenance →

Her2/
neu+
N=536

Lapatinib 1250 daily
+
Paclitaxel 80 D1,8,15 q28d
OR Docetaxel 75 q21d

Trastuzumab IV qw
(load 4mg/kg, then 2mg/kg)
Paclitaxel 80 D1,8,15 q28d
OR
Trastuzumab IV q3w
(load 8mg/kg, then 6mg/kg)
Docetaxel 75 q21d

Lapatinib 1500 daily

Trastuzumab IVq3w
(6mg/kg)

Endpoints

- PFS
- OS, RR, Clin benefit, tox, cardiac tox, QoL, TT
- CNS prog, biomarkers

MA.31 Schema

← Weeks 1-24 → ← Maintenance →

Her2/
neu+
N=536

Lapatinib 1250 daily
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Lapatinib 1500 daily

Trastuzumab IVq3w
(6mg/kg)

Stratified by prior
(neo)adj chemo,
Anti-Her2/Neu therapy,
taxane schedule, liver
metastasis

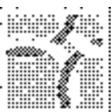
General Principles to NCIC-CTG Pharmacogenetic Studies

- Evaluate clinically relevant outcomes (primary and secondary from main study)
 - May include additional analyses such as PG-PK correlations, PG-gene/protein expression correlations, etc.
- Adjust for relevant clinical + biological prognostic covariates
 - in logistic/linear regression, CPH models, etc.
 - E.g. adjust for quantitative ER/PR status in addition to age, etc.
 - randomization was to therapy, not to genetic variations being studied
 - Validation/replication vs. discovery hypotheses



General Principles to NCIC-CTG Pharmacogenetic Studies

- Collect first
 - Ensure adequate amounts stored for future use
 - Site specific Correlative Studies Working Groups and Executive Committees to control use of specimens
- Complementary analyses
 - Many groups already performing/planning PG studies
 - NCIC-CTG seeks to complement, replicate, and expand on such research
 - Secondary goal – future pooled analyses, replication datasets



Pharmacogenetics of Lapatinib

- Evidence exists for *EGFR*, *ABCG2* polymorphisms affecting toxicity +/- cancer outcomes for gefitinib and/or erlotinib*
- PG/PK studies suggest roles of these genetic variants in affecting PK levels and drug toxicities (GI, skin)

*Rudin et al, JCO 2008; Liu et al, Pharmacogenomics J 2008; Gregorc et al, CPT, 2008; Cusatis et al, JNCI 2006, Li et al Cancer Biol Ther 2007



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- Evidence exists for *EGFR*, *ABCG2* polymorphisms affecting toxicity +/- cancer outcomes for gefitinib and/or erlotinib*
- PG/PK studies suggest roles of these genetic variants in affecting PK levels and drug toxicities (GI, skin)
- Her2/neu data forthcoming from coop group studies



*Rudin et al, JCO 2008; Liu et al, Pharmacogenomics J 2008; Gregorc et al, CPT, 2008; Cusatis et al, JNCI 2006, Li et al Cancer Biol Ther 2007

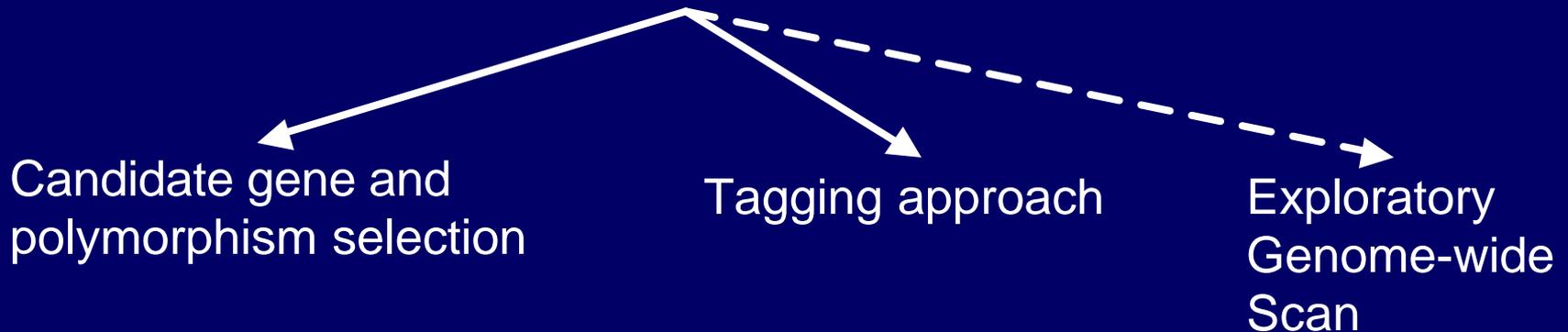
Pharmacogenetics of Trastuzumab

- The Antibody dependent cell mediated cytotoxicity (ADCC) of NK cells/monocytes is affected by polymorphisms of Fc γ RIII antibody receptors.
- Fc γ RIIIa-158 V/V genotype correlated to improved outcome in a small subset of trastuzumab treated breast cancer patients, and correlated to ADCC assay results*

*Musolino et al, JCO 2008

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*Musolino et al, JCO 2008

MA.30 Schema (on hold currently)



**Stratified by #positive LN, prior adjuvant chemo,
trastuzumab use**

Pharmacogenetics of Anastrozole

- For aromatase (*CYP19A1*) gene, in letrozole/advanced breast cancer study, 3'UTR polymorphism was associated with TTP in 67 patients*
- Resequencing of aromatase has been performed, as well as functional genomics of non-synonymous exonic SNPs**
- Other groups are evaluating as well (e.g. Mayo/MD Anderson/PGRN)



*Colomer et al, Clin Cancer Res, 2008

**Haiman et al, Hum Molec Genet, 2003; Ma et al, Cancer Res, 2005;

Pharmacogenetics of Anastrozole

Pharmacokinetic pathways: anastrozole metabolism

Pharmacodynamic pathways: Steroid biosynthesis, metabolism and effect

Candidate
polymorphism⁺
Selection

Tagging approach
To *CYP19A1*

Multi-stage
Genome-wide
Scan ± Replication

*Colomer et al, Clin Cancer Res, 2008

**Haiman et al, Hum Molec Genet, 2003; Ma et al, Cancer Res, 2005;

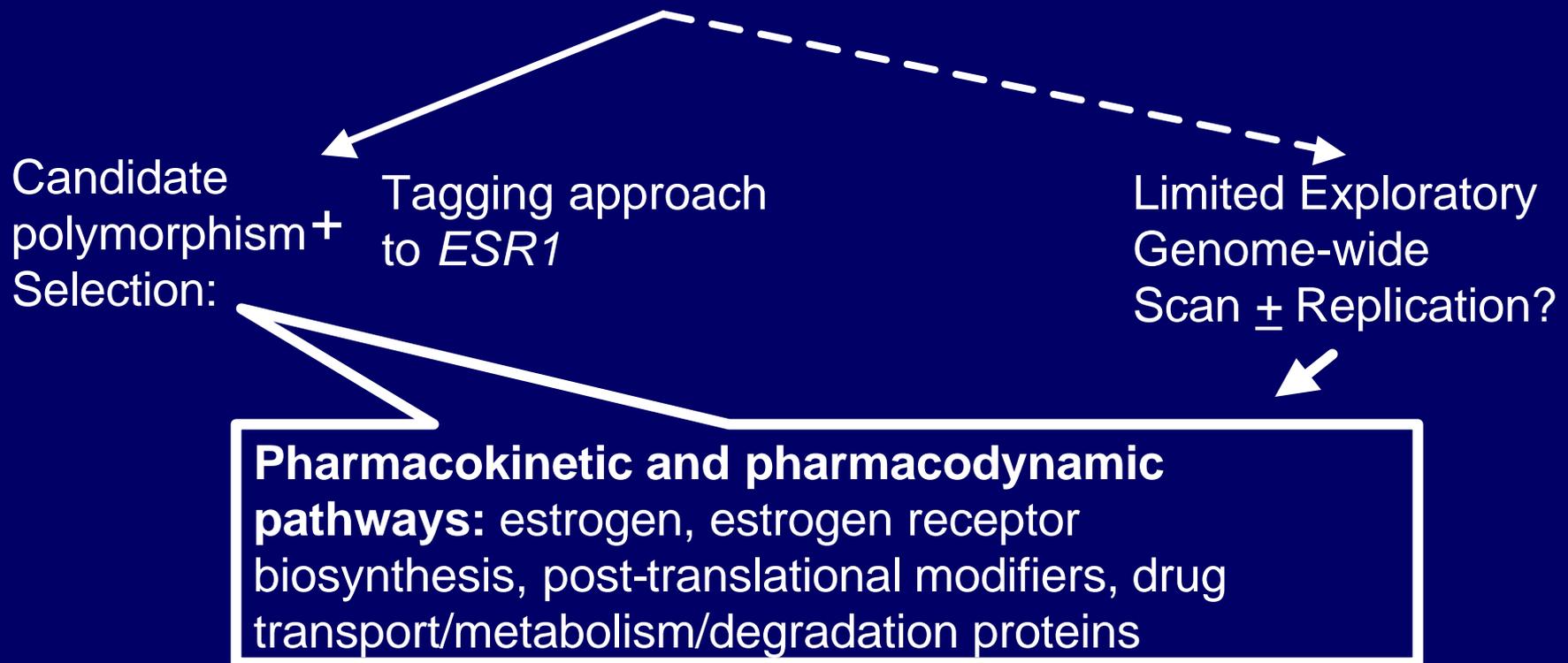
Pharmacogenetics of Fulvestrant

- Little information at present
 - May change by the time main study is completed



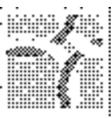
Pharmacogenetics of Fulvestrant

- Little information at present
 - May change by the time main study is completed



The Building Blocks

- Longterm goal: Develop homegrown comprehensive Canadian team of pharmacologists, molecular and classical epidemiologists, translational scientists and molecular biologists, bioinformatics experts, biostatisticians, and clinicians to tackle PG problems → model from molecular epidemiology of risk.
- Loosely link pharmacogenetics researchers across Canada
- Coordinate with recent Pharmacogenetics and Pharmacoepidemiology initiatives at NIH/NCI/DCEG/DCCPS
- Improve lines of communication with Pharmacogenetics Research Network
- Set as priority the collection of blood samples for all Phase II/III studies
- Coordinate sample collection, processing and storage according to CTRNet/Marble Arch guidelines
 - Visiting SWOG blood repository in Buffalo
 - Visiting PLCO/NLST repositories in Frederick MD/Colorado



Key Personnel, Pharmacogenetic Studies

R. Meyer (NCIC-CTG Director)

K. Gelmon (breast site group leader and PI, MA.31)

K. Pritchard (PI, MA.30)

S. Chia (Correlative Sciences Coordinator, MA.30)

S. Aparicio (Correlative Sciences Coordinator, MA.31)

L. Shepherd (Specimen Biorepository)

J.A. Chapman (Biostatistics)

T. Whelan (Trial Committee Member, QoL Studies)

W. Parulekar (Physician Coordinator, MA.31)

